EXOPHTHALMOS ASSOCIATED WITH DIABETES INSIPIDUS AND LARGE DEFECTS IN THE SKULL BONES

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In November, 1927, C. C., an Italian boy, aged nearly four years, was admitted to Bellevue Hospital, and assigned to the Eye Service because of marked exophthalmos. I recognized him immediately as a patient I had examined at Mount Sinai Hospital about three months before, through the courtesy of Dr. Isadore Goldstein. Fortunately the diagnosis of Schüller's disease (or Christian's disease) had been made at Mount Sinai Hospital before I saw the patient, for I was unfamiliar with the striking syndrome presented and should not have been able to classify it. The case in its earlier stages has been reported by Dr. Louis Hausman and Dr. Walter Bromberg in the Archives of Neurology and Psychiatry, June, 1929.[1]

Pronounced exophthalmos has been the most striking clinical feature in the reported cases, but seemingly the attention of ophthalmologists has not been called to the condition by description in eye literature. Moreover, no reference can be found to an antemortem orbital dissection in a case demonstrating the syndrome, and so for the first time I can report surgical exploration of the orbit in a living victim of this rare and important disease, and definitely establish the cause of the extreme proptosis.

In September, 1905, Dr. Thos. W. Kay[2] presented a patient before the Medical Society of Pennsylvania and read a paper entitled "Acquired Hydrocephalus with Atrophic Bone Changes, Exophthalmos and Polyuria." The patient

was a seven-year-old boy who had had scarlatina three years before. Eighteen months before the case was presented, exophthalmos made its appearance and progressed steadily. The author said the exophthalmos was so pronounced that the eyes had to be protected by wearing a handkerchief over them, as they were too prominent for the use of glasses. Four months after the appearance of exophthalmos, polyuria was evidenced. At the time the case was presented the specific gravity of the urine was 1.000–1.001 and the child was passing 23 quarts of urine daily. Large parts of the bones of the skull were soft, and the squamous portion of the right temporal bone gave way a little under pressure with the finger. Dr. Kay expressed the opinion that in this case the possible lesion was situated in or about the floor of the fourth ventricle.

In 1915, Professor Artur Schüller,[3] under the title "Über eigenartige Schädeldefekte in Jugendalter," described three cases, one of which manifested bilateral exophthalmos, large defects in membranous bones, and polyuria. The patient was a five-year-old girl. Schüller was especially interested in the *x*-ray findings of the skull, which he described as "map-like," on account of the transparent spots seen in the *x*-ray pictures. He could palpate pulsating openings. Schüller supposed that the defects in the skull and the diabetes insipidus were caused by disturbance of the pituitary function, and he thought the exophthalmos was occasioned by brain pressure on the orbital contents made possible by the large defects in the anterior fossa of the skull.

In the Osler Memorial Volume of 1919 can be found an article by Dr. Henry A. Christian[4] on "Defects in Membranous Bones, Exophthalmos and Diabetes Insipidus." This article was reprinted in the Medical Clinics of North America, January, 1920.[5] His patient, a five-year-old girl, was studied at Peter Bent Brigham Hospital, in Boston. On account of his excellent description of the condition, the

syndrome is sometimes called Christian's disease. Christian considered the syndrome essentially one of dyspituitarism. He thought the disturbed pituitary function occasioned both the diabetes insipidus and the bone changes. He said: "The most extensive defects are in the anterior half of the skull. Of the frontal bone, particularly the lateral portions, only irregular rather narrow septa of bones are left between the large islands of entire bone disappearance. In a similar way the orbital plates of the frontal bone have largely disappeared so that there is little bony support remaining for the eyeballs." Christian found that pituitary extract controlled the polyuria when given subcutaneously, but that it had no effect on the polyuria when given by other methods. Pituitary extract had no effect on the bone defects or exophthalmos.

In "Defects of Membranous Bones, Exophthalmos and Polyuria in Childhood; Is It Dyspituitarism?" Dr. Alfred Hand[6] recalled the report made by him in 1893[7] under the caption, "Polyuria and Tuberculosis." A boy three years of age was admitted to the Children's Hospital in Philadelphia, December 1, 1892. The child's eyes were in a condition of exophthalmos giving him a frog-like appearance and there was a corneal opacity in each eye. The child was suffering from thirst and was passing 114 ounces of urine daily. The specific gravity was 1.000 and it contained no sugar or albumin. Bronchopneumonia developed and the child died. From a general view of the case, a diagnosis of tuberculosis was made. At autopsy a yellow spot about the size of a five cent piece was noticed about the right parietal eminence. After reading the published report of Kay's case and with increased experience at the autopsy table, and with Christian's case report in mind, Hand doubted whether the tuberculosis had any causal relation to the exophthalmos, polyuria, or defect with yellow spot in the parietal bone. He described another case of a four-year-old

boy who had exophthalmos and skull defects, but who at that time had no polyuria.[6] Hand adopted Schüller's suggestion that the exophthalmos was due to involvement of the orbital plate of the frontal bone, but also advanced the theory that "the primary process might be neoplastic, benign and myxomatous in character, affecting for some unknown reason the membranous bones and producing exophthalmos and polyuria secondarily by pressure."

Under the title "Defects in Membranous Bones, Exophthalmos and Diabetes Insipidus," Thompson, Keegan, and Dunn,[8] of Omaha, gave a report of their painstaking study of a nine-year-old boy who manifested the typical syndrome. The boy died and the authors were then able to give a detailed account of the autopsy findings, but apparently the orbit was not studied at autopsy. "In the center of the largest membranous areas there was yellowish fibrous tissue and the inner surface of the dura was mottled by a yellowish tissue. Microscopic section through the region showed a lining layer of large oval cells with sharp borders, with clear, slightly granular cytoplasm and small compact centrally placed nuclei. The cytoplasm contained a variable amount of lipoid material in finely divided form." Death was ascribed to cardiac failure attributed to impaired circulation, incident to extensive pulmonary fibrosis. The authors say that "the faulting of the frontal bones with its orbital plates fully explains the exophthalmos." They stress the importance of early involvement of the tuber cinereum, and dyspituitarism as a cause of the syndrome was excluded by the absence of material pathologic changes in the hypophysis. Pathologic support was given to current work on experimental polyuria which puts the lesion of diabetes insipidus in the hypothalamus. From clinical behavior and pathologic findings, the authors judge that an infectious etiology is more likely than a primary metabolic endocrinologic disturbance.

Grosh and Stifel[9] reported the case of a seven-year-old girl who came under observation June 27, 1919, in Toledo. In addition to marked defects in the bones of the skull, diabetes insipidus, and a definite left exophthalmos, there was some degree of dwarfism. The authors called attention to the work of Bremer and Bailey, showing that polyuria found in experimental lesions at the hypophysis is usually temporary, while lesions of the hypothalamus produced a permanent polyuria.

Under the title "Defects in Membranous Bones, Diabetes Insipidus and Exophthalmos," Denzer[10] briefly reported a case in 1926. It was a four and one-half year old boy manifesting defects in the skull bones a year before polyuria was discovered. Denzer said the exophthalmos was due probably to defects in the bones of the orbit.

In the Transactions of the Australian Medical Congress in 1927, Stowe[11] reported a case of "Diabetes Insipidus Associated with Defects in the Skull." The clinical picture was diabetes insipidus with exophthalmos. Stowe considered that the skull should be *x*-rayed in all cases of diabetes insipidus in children. His report was very brief. Later, Milne reported the same case more in detail to Rowland. An autopsy was performed, and "on reflecting the scalp a number of swellings resembling putty in appearance, but of fairly firm consistency, were observed. These areas were extensions, through small perforations in the skull, from the dura, which was extensively infiltrated. The brain was normal. A compact yellow mass about the size of a walnut rose up out of the sella turcica displacing the hypophysis but without eroding or distorting the clinoid processes. Another mass projected back from the right wing of the sphenoid which was extended to the ethmoids and both orbits." The histologic description of this tissue was, "striking yellow mass composed of spindle cells with large clear spaces filled with granular yellow substance. Scattered

throughout the tumor were giant cells with rosette nucleus surrounded by a granular zone. The nodules from the dura showed the same changes. The entire pituitary was invaded by the yellow growth." Milne thought the condition due to a tumor arising in the hypophysis. No report was made of the rest of the body. In a personal communication, Dr. Rowland says that the tissue was examined by Dr. Lynch, of New Zealand, who reported, "I am not able to say whether the condition is a primary tumor of the hypophysis or whether the invasion of the sella turcica is secondary. The condition is best described as chordoma." Dr. Lynch considered xanthoma as a possible diagnosis.

In 1926 Kyrklund[12] published a case report and gave autopsy findings. The patient was a girl, aged twelve years, who at four years of age developed thirst and polyuria. The cranium showed numerous defects. There was exophthalmos, but it excited no more interest or curiosity than had been shown in the study of other patients exhibiting the important syndrome, the outstanding clinical feature of which is exophthalmos. The autopsy revealed erosion of the skull and brownish-yellow material in the defective areas. The hypophysis did not show pathologic changes, but there were brownish-yellow growths in the brain stem behind the hypophysis, as occurred in other cases. The lungs showed extensive changes. Apparently no explanation for the exophthalmos was sought for, but Kyrklund thought that the growths were of "sarcomatous" nature and that the new-growths in the region of the hypophysis accounted for the diabetes insipidus.

Schüller[13] manifested interest in the syndrome to which his name is sometimes attached by reading before the first International Congress of Radiology in London, in 1925, a short article on "Dysostosis Hypophysaria." In this article he reviewed his cases reported in 1915 and spoke of cases reported by Christian, Hochstetter, and Alberti, but his

interest did not carry him far into the literature or into the pathology of the condition. His summary was as follows: "There exists a peculiar type of defects of the skull, characterized by the multiplicity, the great size and the sharp outlines of the defects localized as well on the cranium as on the base of the skull, combined with defects in the pelvis, exophthalmos, and with some of the symptoms generally diagnosed as due to pituitary underfunction, namely, dwarfism and diabetes insipidus. I propose for this symptom complex the name Dysostosis Hypophysaria."

In the November, 1928, number of the Archives of Internal Medicine may be found a most interesting article by Rowland,[14] of Detroit, entitled, "Xanthomatosis and the Reticulo-Endothelial System: Correlation of an Unidentified Group of Cases Described as Defects in Membranous Bones, Exophthalmos and Diabetes Insipidus (Christian's Syndrome)." He reports in detail two cases of the syndrome under discussion, one of which came to autopsy. His first patient was a white boy, aged five years. Examination of the eyes showed "marked exophthalmos, greater in the right eye. The eye turned downward and inward. Pupils were slightly dilated, regular and equal, reacted to light and in accommodation. The muscle response was normal and nystagmus was not present. The fundi appeared normal; the discs were well defined and the vessels were normal in size and appearance." At autopsy there was "marked exophthalmos of the type seen in cavernous sinus thrombosis. . . . Palpation of the skull revealed many cranial defects in which the bone appeared to be missing. . . . When the head was opened, the scalp was found normal in appearance. When the calvarium was exposed, there were numerous annular defects of the cranial bones which varied in size from 0.75 to 4 or 5 cm. in diameter. These defects had slightly wavy edges, but were fairly sharp. The bone at the margin was firmer than normal and the defect itself

was filled with a gummy, semicaseous bright yellow tissue of rubbery consistency. . . . When the base of the skull was inspected, it was found irregularly covered over with these yellowish granulomatous swellings which had destroyed a large portion of the bone of the base, extending forward into both orbits and completely surrounding the region of the hypophysis and destroying the sella turcica. . . . The lungs were voluminous and felt fibrous to palpation. The left lung was somewhat adherent over the posterior lateral aspect of the costal pleura, the adhesions being of the same peculiar yellowish gummy nature that was noted in the granulomas of the skull." The pathologic report was by Dr. A. S. Warthin, and he said that "the dural plaques consisted of masses of lipoid containing cells of reticulo-endothelial type resembling xanthoma. Throughout were numerous multinuclear giant cells. . . . These plaques did not suggest infectious granuloma but resembled xanthoma or masses of cells of the xanthoma type, and probably consisted of proliferated reticulo-endothelial cells with cholesterolosis. Fat stain showed cells to be loaded with lipoids." Dr. Warthin gave no report of examination of tissue from the orbit.

Rowland's second case was a white boy, aged three years, eleven months. In this case the ophthalmic examination was made by Dr. Parker Heath: "On April 24, 1926, examination showed vision in each eye, as determined by objects, normal for distance and near. Convergent power normal; no paralysis of extrinsic muscles. Pupils equal in diameter and react promptly to light and in accommodation; consensual reflexes are present. The left eye is slightly more prominent than the right, being proptosed approximately 2 mm. There is none of the lid-lag sign found in exophthalmic goiter. Neither globe is congested. Ophthalmoscopic examination of the right eye: Pupil dilates evenly, media clear, disc normal in color, rings slightly blurred,

vessels normal in caliber and course, foveal reflexes present. The left eye is essentially the same. The mechanism of the exophthalmos, judging from the *x*-ray plates, may be due to letting go of the apex of the orbit, as suggested by a previous observer."

Rowland thinks the cases represent a form of xanthoma in which many parts of the reticulo-endothelial system show storage of lipoid or hyperplasia of lipoid cells. He discusses the group of cases described by different authors and thinks that they represent the same condition. He says that "the researches on this subject indicate that all the varied manifestations of xanthoma can be brought back to the single pathologic principle that certain substances infiltrate the reticulo-endothelial system. The xanthoma cell is a cell of reticulo-endothelial origin infiltrated with lipoids. Xanthoma lesions are the hyperplastic reaction of the reticulo-endothelial system, resulting from the infiltration of lipoids in excess in the body fluids. A localization of this process produces the hyperplastic nodular lesions. . . . The study of this series of cases in which hyperplasia of the lipoid cells occurs both as a diffuse process in various organs and as localized nodular lesions clears up in a surprising way the mystery of the destruction of bone, exophthalmos, diabetes insipidus and dwarfism in the syndrome." Rowland also states that—"One is not dealing with true neoplasms, but with hyperplastic new formations, *i. e.*, lipoid storage tumors. The formation of these nodules is a compensatory act on the part of the body in its attempt to rid the blood of an excess of lipoid which cannot be properly excreted."

"Christian's Syndrome and Lipoid Cell Hyperplasias of the Reticulo-Endothelial System" is the subject of another paper by Rowland[15] published in June, 1929. He says, "In rapid development the infiltration is diffuse. In slow development the change is more localized, assuming at times a tumor-like appearance. In the course of time, there is

fibrosis, occasionally necrosis and cyst formation which mask the original picture."

February 27, 1929, Hausman and Bromberg[1] submitted for publication in the Archives of Neurology and Psychiatry a paper entitled "Diabetic Exophthalmic Dysostosis." They reported in detail the early study of the patient who later was admitted repeatedly to Bellevue Hospital on the eye service, and who was operated on there. It is evident that the pathologic condition had been progressing over a period of three years, and the advance in the condition revealed itself principally in the increased exophthalmos and in the pathologic ocular changes. The authors give a careful review of the literature and make interesting comments on the sex, age, pathogenesis, pathology, and symptomatology of the syndrome. They call attention to the difference of opinion as to whether the diabetes insipidus is caused by a lesion of the posterior lobe of the pituitary body or one of the tuber cinereum, but they think diverse views on this point can be reconciled, as the posterior lobe of the pituitary body, the stalk, and the tuber cinereum in all probability constitute a physiologic as well as an embryologic and anatomic unit. They raise the question as to whether these parainfundibulum structures may not be responsible in some measure for the atrophic control of bone and they hint that the pathologic condition of the same structures may occasion the defects in the skull bones. They emphasize the high incidence of antecedent infection in the cases of Christian's syndrome which they studied. They say "particular significance is attached to the dysostosis in relation to the mechanism of diabetes insipidus."

CASE REPORT.—C. C., a boy, aged nearly four years, of Italian parentage, was admitted to the eye wards of Bellevue Hospital November 22, 1927. He had previously been admitted to Mount Sinai Hospital July 19, 1927. Then he had been re-admitted to Mount Sinai August 21, 1927. The dates of later admission to

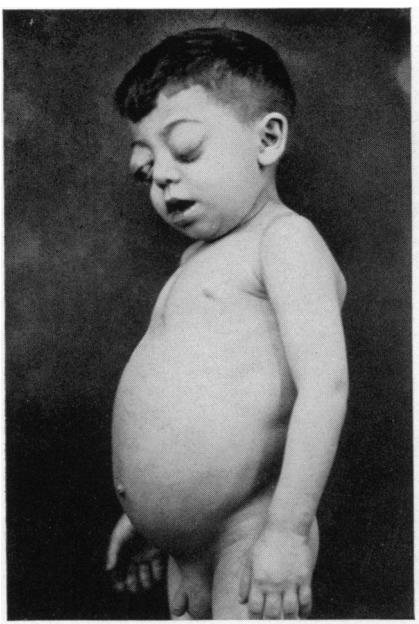

Fig. 1. — Photograph of C. C., aged five years, to show general appearance. Note posture, large abdomen, open mouth, extreme exophthalmos. Two adhesions have been introduced at lid margins on each side to prevent complete prolapse of eyeballs. One adhesion had been cut on right side.

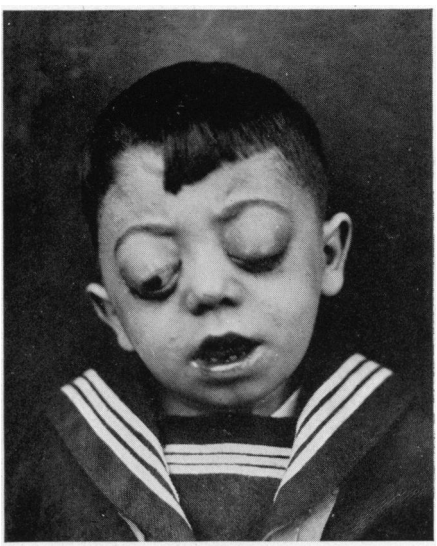

Fig. 2. — Right eye is displaced downward as well as forward. Right ear displaced downward by neoplastic invasion of region of temporal bone. Interpalpebral adhesion to prevent exposure of cornea, one at temporal margin of right eye, one at nasal margin, and one at temporal margin of cornea of left eye.

Bellevue on the eye service were November 26, 1928, and April 22, 1930. During the period between November, 1927, and April, 1930, he was seen occasionally in the Bellevue outpatient clinic. At the time of his first appearance at Bellevue Hospital the parents said that they noticed the prominence of the right eye about two years before and that of the left eye about a year later. The right eye had continued more prominent than the left and the prominence had persisted in getting worse. The parents said that unusual thirst and frequent urination began about the same time that the right eye began to bulge. The father thought that the child was all right until he had measles, and that the present condition was due to the measles. Except for the eye prominence, the constant thirst, and the frequent passing of urine day and night, the parents thought the boy normal in every way.

The child appeared rather apathetic, with open mouth and listless expression. He carried his head slightly toward his right shoulder, and his right ear was noticeably lower than the left. He had a "frog-like" expression, due to the prominence of his eyes and the flattened appearance of his forehead. He was slightly stooped, and his abdomen was large. The genitalia were normal. He appeared to see well and hear well and he seemed normally bright for his age.

The motility of the eyes was good. Pupils were round. The cornea, iris, lens, and vitreous were normal in each eye. Examination was made under ether anesthesia. Tension (Schiötz): right eye 18 mm. Hg and left eye 20 mm. Hg. Exophthalmometer readings were: right eye 24 mm. and left eye 23 mm. The fundi appeared normal except for slight congestion of the retinal veins and slight edema at the discs. There was no measurable elevation. There was a moderate squamous blepharitis. The proptosed eyes could not be put back in position by pressure and they did not pulsate.

Palpation of the head demonstrated areas of decreased resistance to pressure. The areas were not really soft, and seemed neither elevated not depressed. No pulsation could be felt over the rarefied areas. No bruit could be heard with the stethoscope applied anywhere on the head.

Laboratory Reports: Wassermann tests were negative for blood and spinal fluid. The urine was negative except for low specific gravity (1.004). The blood was normal.

X-ray examination showed striking defects in the skull bones,

more on right side than on left. All the bones showed material losses, but those about the right orbit and the right temporal bone were most marked.

The little fellow went about the wards and corridors with a tin cup in his hand, asking everyone for a drink. He was always wet, due to copious urination. He seemed content, apparently free from pain. He ate well and slept well, except that his thirst led him to waken occasionally and ask for a drink of water.

The second admission was on November 26, 1928. The general condition seemed about as before, but the exophthalmos had increased markedly and the epithelium of the cornea of the right eye was broken. As the sight was endangered, it was decided that the lid margins should be kept nearly approximated. Accordingly the child was put under ether and preparations for adhesions between the lid margins were made. The marginal epithelium was removed from corresponding areas on the upper and lower eyelids near the outer and inner margins of the corneas of both eyes. Sutures were introduced to hold the denuded areas in apposition.

While the patient was under anesthesia the eyes were examined. The exophthalmometer readings were: right eye 35 mm. and left eye 33 mm. This represented a startling increase of proptosis in one year, as the readings in November, 1927, were 24 mm. for the right eye and 23 mm. for the left. The eyegrounds looked about as they did a year before, with a little edema at the papillae, but with too little elevation for measurement.

X-ray examination showed larger defects of the skull bones, but none in the long bones.

The polydipsia seemed worse in that the child asked for water more often, especially at night. The specific gravity of the urine was 1.002. Under subcutaneous injections of pituitrin the output of urine approached normal and the abnormal thirst disappeared. It was not possible to get an accurate estimate of the amount of urine passed, because of the established uncertain habits of urination.

At this period the spinal fluid was found normal and the Wassermann reaction again negative. The blood calcium and phosphorus were reported normal.

The operative procedure for the production of lasting adhesions to hold the eyes nearly closed was a success, and the patient peeped out through the slightly separated eyelids.

On April 28, 1930, the patient was admitted to the hospital for the

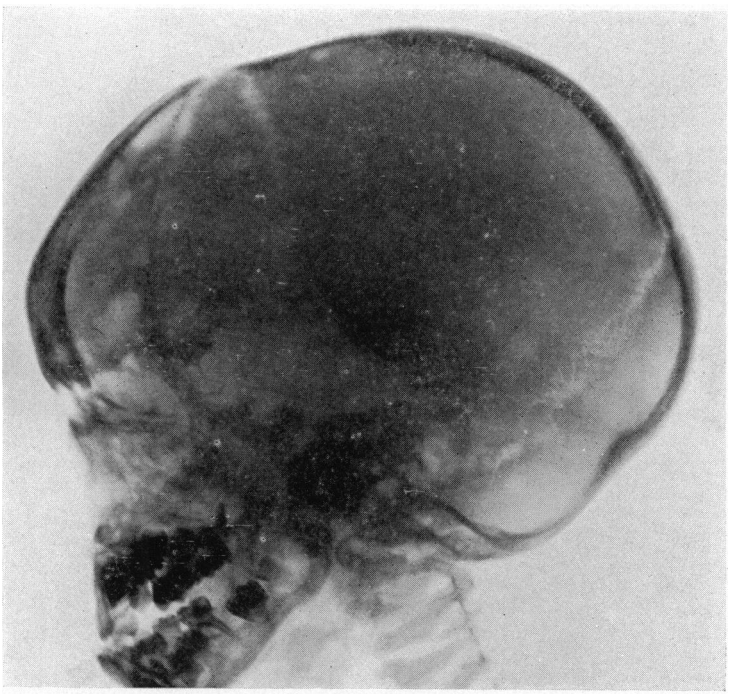

Fig. 3.—X-ray of skull, showing large defects due to loss of bone, especially wholesale destruction of bone in orbital region.

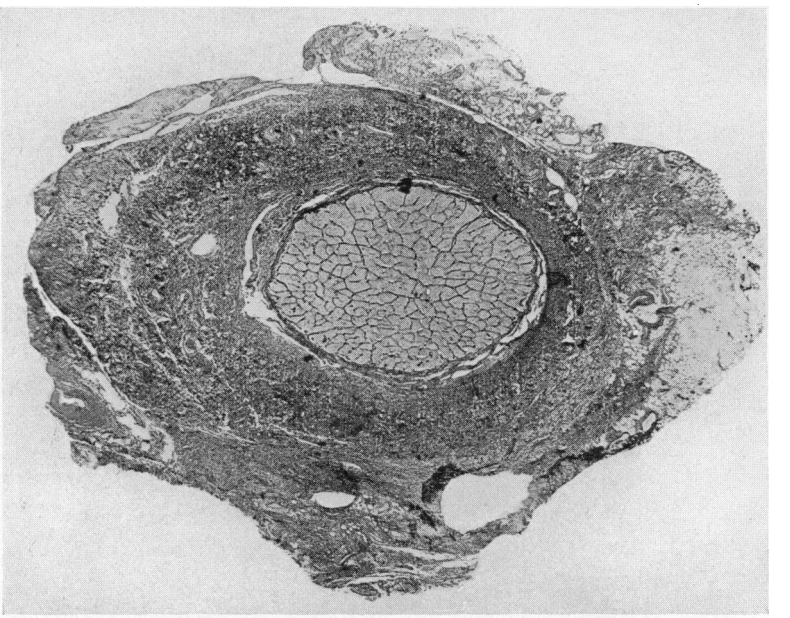

Fig. 4.—Section of retrobulbar growth, showing optic nerve completely enclosed in large nodule of new-formed tissue. Specimen taken from right orbit. (Preparation by Dr. A. E. Town.)

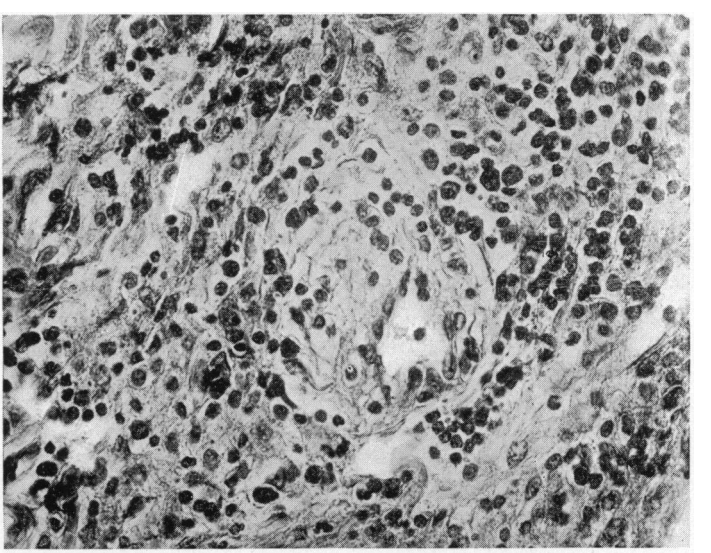

Fig. 5.—Photograph of high-power microscopic appearance of tissue from a neoplastic-like nodule of right orbit. Resembles postmortem tissue described by Rowland and Warthin (xanthomatosis). (Preparation by Dr. A. E. Town.)

third time. Since the child was last in the hospital, one of the members of the attending staff had cut the inner adhesion of the right eyelids and partly liberated the eye, as shown in the photographs. The right eye showed not only extreme proptosis, but marked depression as well, and there was very little motility in any direction. The movements of the left eye seemed unimpaired. The pupils were semidilated and reacted only slightly to light. Lateral nystagmus had developed, so impairment of central vision was suspected.

X-ray exposures showed progression of the bony losses in the skull, and also a defect in the iliac fossa of the right innominate bone.

The blood Wassermann was again negative. The hemoglobin was 65 per cent. Erythrocytes, 3,456,000; leukocytes, 7,900; polynuclears, 69 per cent.; lymphocytes, 28 per cent.; large monocytes, 3 per cent. The blood calcium was 12.1, and the weight, 27 pounds.

The father had noticed that the boy was not seeing so well as formerly, so he urgently requested that we cut one of the adhesions to liberate the left eye, as had been done for the right eye. Ether was given and the nasal adhesion on the left side was cut. Opportunity was again afforded for examination under anesthesia. The interior of each eye appeared almost identical. The cornea of the right eye showed slight opacity. Otherwise the anterior structures were normal. The vitreous had dust-like and fine membranous opacities. The retina showed changes, unobserved before. The veins were dilated and tortuous. The papillae were pale, but still slightly edematous. There were numerous punctate hemorrhages scattered through the background, but particularly in the macular regions, accounting for the apparent reduction of central vision and the nystagmus. The optic nerve involvement was considered a factor, too. There were markings to indicate that the leakage had been going on for some time. The pupils were dilated and reacted only very slightly to light. Palpation revealed a defect in the orbital margin above. Deep orbital palpation demonstrated a firm, non-pulsating, movable, nodular mass about 1 cm. in diameter resting on the floor of the orbit near the temporal wall. A smaller mass could be felt near the roof of the orbit. On the left side a defect in the orbital margin and anterior part of the roof could be felt.

While the child was completely under ether, removal of some of the new-formed material from the right orbit seemed proper. A free

incision was made along the orbital margin below and the orbit was entered. Normal fat presented, but there was no difficulty in finding and removing the large nodule that had been felt on the floor of the orbit. Then it was found that the orbital cavity was nearly full of the extraneous nodular material and that the optic nerve was completely enclosed by it. A piece was taken, including the nerve. The masses were distinctly yellow, and had a rubbery feeling. There is no previous record of excision of material from the orbit of a living victim of Christian's disease, but the material removed at operation answered to the description of that removed at autopsy in Rowland's case. It is worthy of note that the shape and size of the orbital cavity seemed normal and that the periosteum seemed intact. While it was easy to determine that there was large loss of bone from the orbital walls, because of decreased resistance to pressure, it was plain that there was no bulging of periosteum into the cavity of the orbit, no pulsation, and no evidence to support the accepted theory that loss of bone explained the exophthalmos. There was definite evidence that the expanding new-formed masses had crowded the eyeball forward, just as a carcinoma, a cyst, or an abscess would have done in the same orbit. Postoperative healing was uneventful.

Dr. Douglas Symmers submitted the following report on the tissue: "Microscopic examination of the tissue removed from the eye in the case of C. C. shows the presence of an infiltrating tumor made up of large cells of variable shape with a sharply defined limiting membrane, a clear or finely foamy cytoplasm, and a small, rather richly chromatic nucleus. In other words, the cells are morphologically identical with those of the so-called chordoma, but at the same time they resemble embryonal fat cells or xanthoma cells. Frozen sections of tissue removed from the tumor, however, and stained with Sudan III, while showing large quantities of intercellular infiltrating fat, fail to reveal the slightest indication of fat or fat-like substances in any of the tumor cells themselves. For this reason I think that the embryonal fat and xanthoma cells can be safely eliminated. The morphology of the tumor growth, together with its location at the base of the skull, combine, I think, to establish the diagnosis of chordoma; that is to say, of a tumor arising from embryonal cartilage cells retained in the body as remnants of the notochord, which in the embryo consists of a rod of cartilage cells constituting the foundation of the axial skeleton. It extends throughout the entire length of the future vertebral column and

reaches as far as the anterior end of the mid-brain, where it ends in a hook-like extremity in the region of the future dorsum sellae of the sphenoid bone. The tumor springing from these embryonal cartilage rests is not at all common, but is perhaps most frequently seen as an infiltrative and destructive growth of the bones in the vicinity of the sella turcica and elsewhere in the skull."

In a personal letter, Dr. Russell S. Rowland said, "The section consists of a cross-section of optic nerve surrounded by granulomatous-like infiltration of the type characteristic of Schüller-Christian's disease. The infiltration consists of large lipoid-containing xanthoma cells, proliferating fibroblasts and lymphocytes. This case is identical histologically with that already reported by myself. It is of interest to mention that in the case described by Dr. Milne, of New Zealand, the pathologist's report was chordoma with xanthoma questioned. My own pathologist, Dr. Plinn F. Moorse, of Harper Hospital, states that the cells of a chordoma are quite different from these lipoid-containing cells, frequently resembling young cartilage cells."

COMMENTS

1. Exophthalmos, large defects in the skull bones, and diabetes insipidus make up a syndrome of interest to all clinicians. It is of especial interest to pediatrists because it occurs in children. It is of prime importance to ophthalmologists because the striking tell-tale sign is the exophthalmos, and because the optic nerve and retina may become involved, with consequent impairment of sight. The exophthalmos may be so great that impairment or loss of sight may result from exposure of the cornea.

2. Given a child with unilateral or bilateral exophthalmos without evident cause, the ophthalmologist may well think of the possibility of Christian's syndrome. Let him palpate the skull for possible defects in the bone, particularly around the orbit. Let him subject the patient to *x*-ray examination of the head, and of the hip bones if he wishes, and the radiologist may demonstrate areas of bone loss that cannot be discovered by palpation. Let him think of the possibility

of great thirst, of excessive urine of low specific gravity (diabetes insipidus). With the condition well in the ophthalmologist's mind the diagnosis of the syndrome is easy.

3. Wassermann tests of blood and spinal fluid have not been positive in any case. Tuberculin tests have been done in only a few cases, but there seems to have been no positive report.

4. Chemical examination of the blood reveals nothing characteristic. Examination of the cellular elements of the blood may show no abnormalities. In this regard there is quite a contrast with such a condition as chloroma.

5. At present we are justified in thinking of a neoplastic or neoplastic-like process involving structures in the floor of the third ventricle (tuber cinereum, infundibulum), possibly implicating the hypophysis and other nearby cerebral structures, invading the orbit, and involving the bones of the skull and perhaps other bones. The infiltrating and destructive tissue need not be of a single pathologic class, but it is most likely to be the yellow, nodular, lipoid storage xanthoma that Rowland has held responsible for this vicious process which occurs in children.

6. With reasonable assurance the diabetes insipidus can be accounted for by disturbance of the cerebral tissue in the floor of the third ventricle, with or without invasion of the hypophysis. The bone defects probably are not the result of interference with function of these same cerebral structures, but are due to true invasion of the bones by the hyperplastic process. The pronounced exophthalmos is probably never due to mere loss of bone of the roof and other bony parts of the orbit, but to true invasion of the orbit by the hyperplastic process.

7. Invasion of the hypophysis may occur with or without erosion of the sella turcica. If the hypophysis is injured, asexuality, dwarfism, and other evidences of interference of function may result.

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DISCUSSION

DR. PARKER HEATH, Detroit: I want to thank Dr. Wheeler for the request to discuss his very interesting case. With Dr. Rowland, I have had opportunity to study two cases. The first was seen at necropsy in January, 1926, and the second in February of the same year. The second case has recovered from the disease. Dr. Rowland has unearthed about thirty cases in the literature, reported from the pediatric side, the radiologic side, and general pathology. Strange to say, eye literature is apparently exempt from reports of these cases. The two I mention are in the current issue of the pre-session volume of the American Medical Association, and will be given in Detroit in June.

Our prime interest, of course, is the exophthalmos. I agree with Dr. Wheeler that a mass in the orbit is probably the main cause of exophthalmos. At least one case has been reported wherein there was nothing but the mass in the orbit at autopsy, but there have been other cases reported wherein the exophthalmos was symmetrical at first, with no impairment of vision, no obvious changes in the fundus, and may have been due partly to the easing forward of the apex of the orbit.

Studies, pathologically speaking, have shown a diffuse reticular change, or one in which the reticular system was involved, and the peculiar pictures seen in isolated cases, such as exophthalmos, diabetes insipidus, myocarditis, involvement of the long bones, and so on, are a part of the masquerade presented by this diffuse disease. Dr. Rowland's conception is that the disease is primarily reticular and that other manifestations are secondary. In other

words, it is a lipoid disease and it is so diffuse that we see only the outstanding picture. A xanthoma in the lid is just as much a part of the disease as is the exophthalmos from orbit deposits. In other words, fat metabolism is concerned, and that is different in the child than it is in the adult. In the adult lipoid metabolism disturbances may lead to isolated deposits, and in the child there are liable to be diffuse changes leading to this pathologic picture of Schüller-Christian syndrome or Gaucher's disease.

General medical literature is now active in reporting reticular diseases. There are many references to them; but the ophthalmic side is relatively quiet. A thorough study of the reticular system in connection with the eye, I think, will be the threshold of a future reclassification of some of the very obscure manifestations of deposits in the eye.

DR. T. B. HOLLOWAY, Philadelphia: I have not observed a case of this character, but about a year ago my attention was called to the condition by an article in the Archives of Neurology and Psychiatry, and inasmuch as it emanated from New York and from the Mt. Sinai Hospital, it is possible that it pertained to the same patient now described by Dr. Wheeler. Having always been interested in intracranial conditions, I naturally had some slides made which I have used during the past year.

One is impressed by the analogy between these cases and certain types of craniostenosis. The latter has much the same type of symptoms, namely, exophthalmos, impaired vision due to postpapillitic atrophy, nystagmus, and not infrequently there are associated congenital malformations, such as extra digits.

I was also interested because I thought this dysostosis added another intracranial cause for exophthalmos, but Dr. Wheeler has spoiled this by his excellent observation in determining that after all this exophthalmos is not dependent upon and is not caused by malformation of the orbit, as is the case in craniostenosis, but is due to tumor formation originating from the middle fossa of the skull. It is possible that some of the cases of craniostenosis have really been of this type. It is true that in these cases an associated diabetes insipidus is in no sense the rule. It will be recalled that various theories have been offered to explain the bone changes in craniostenosis, and I believe it was Fletcher who suggested that they might be dependent upon a lesion of the pituitary body.

DR. JONAS S. FRIEDENWALD, Baltimore: I should like to call attention to one other ophthalmic condition which may be related

to this congenital defect, namely, amaurotic family idiocy. As you all know, in amaurotic family idiocy there are swollen ganglion cells in the retina and in the brain which contain large amounts of lipo-protein. This fact alone would not relate it to the condition we are discussing, but there has been one case reported by Pick and Bielschowsky,* in which, in association with amaurotic family idiocy, there were the visceral changes of Gaucher's disease. This would seem to form a link between these two types of disease. I think the suggestion of Dr. Heath is correct—that a more thorough knowledge of the lipoid metabolism of the infant will help us to solve the relationship of these remarkable conditions.

DR. JOHN M. WHEELER, closing: I should like to say that probably Dr. Holloway did see a report of this case. Denzer reported a case from Mount Sinai Hospital in 1926, and then about a year and a half ago, before the American Neurological Association, Hausman and Bromberg reported this case, so the case was published from Mount Sinai Hospital.

The patient I am describing also was admitted to the New York Eye and Ear Infirmary in the spring of 1927, just before I saw him at Mt. Sinai Hospital. The condition was diagnosed exophthalmos and the patient was sent to Dr. Dixon for *x*-ray, and he gave me this report:

"C. C., referred here from Dr. Bell's clinic, March 1, 1927. Patient was examined, but the result of the *x*-ray examination was unsatisfactory. We have the films, but they give little or no information."

Some of the members of the Society saw the patient at a meeting of the New York Ophthalmological Society while he was a patient at Bellevue Hospital.

One of the striking things about this, particularly in connection with the cause of proptosis, is that while we can feel the skull defects in this case, we feel no pulsation through the fibrous tissue which separates the brain from the scalp, as this area does not pulsate at all. Apparently there is no increased intracranial pressure, and that makes it rather unlikely, I think, that the extreme proptosis characterizing these cases can be caused by the weight of the brain on the orbit, or even by the loss of tissue at the apex. It seems to me it is much more likely that in the orbit there is always a tumor-like condition.

* Ueber lipoidzellige Splenomegalie (Typ. Niemann-Pick) und amaurotische Idiotie, Klin. Wchnschr., 1927, vi, p. 1631.

The disease is strikingly one of infancy. A few cases of this condition, or one similar, have been reported in youths, but most of the cases that truly belong to this classification are reported in babies. It seems to me altogether likely that the origin of the hyperplastic tissue, at least in some of them, is from embryonal cells, and that they originate in the region just behind the hypophysis, and so destroy the function of the tuber cinereum and other structures about the infundibulum and stalk of the hypophysis; that then diabetes insipidus is likely to show itself and other evidence of interference with vegetative function. It is also possible that different forms of tumor which originate in this particular location may give this syndrome, may destroy the bone in the region of the hypophysis, may invade the orbit and cause proptosis, may cause diabetes insipidus and the rest of the syndrome. It may show different manifestations in different patients, but I think the condition is essentially one of tumor or tumor-like formation.

DIPHTHERIA OF THE CONJUNCTIVA

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One of the most violent, but fortunately one of the rarest, of conjunctival infections is that caused by the Klebs-Loeffler bacillus. I have seen two such cases, with positive cultures, both in infants. Textbooks describe two forms of diphtheritic conjunctivitis. The superficial or croupous is characterized by the presence of a grayish-white membrane which adheres closely to the conjunctiva. Beneath it the conjunctiva is found greatly swollen and reddened, with areas of bleeding. The course of the disease lasts about two weeks, when the membrane will have disappeared without leaving any permanent changes in the conjunctiva. The